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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,191	09/15/2003	Minxue Zheng	1300-0007	9085

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EXAMINER	
CALAMITA, HEATHER	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,191	ZHENG ET AL.	
	Examiner	Art Unit	
	HEATHER CALAMITA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *19-25 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 26-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 1-39 are currently pending. Claims 19-25 and 35-39 are withdrawn as being directed to non-elected subject matter. Claims 1-18 and 26-34 are under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Interpretation

2. Claims 1-18 and 26-34 are product claims directed to primers and nucleic acid constructs. The claims include functional limitations and recitations of intended use that are dependent on the particular target nucleic acid sequence that the claimed primer is intended to copy or amplify. However, no specific target sequences are specified. Therefore, such functional limitations and recitations of intended use confer no structural limitations to the claimed primer. As written, the claimed primer is anticipated by any prior art primer for which a target sequence exists such that the functional limitations and intended uses recited in the claims are fulfilled.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9, 10-14, 26 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Honeyman et al. (AJVR, 1999, cited in the IDS).

With regard to claims 1 and 32, Honeyman et al. teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure

forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see p 735 under *Materials and Methods*, where the primer of Honeyman is complementary to the target sequence. See the diagram below where the primer of Honeyman inherently meets all of the functional limitations when the appropriate target is present) and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see diagram below, where the primer of Honeyman inherently meets all of the functional limitations when the appropriate target is present).

With regard to claim 2, Honeyman et al. teach the site of interest is a nucleic acid sequence (see p 735 under *Materials and Methods*, where the target is canine DNA).

With regard to claim 3, Honeyman et al. teach the site of interest is a single nucleotide polymorphism (see Figure 3, where an adenine residue is replaced by a guanosine residue).

With regard to claim 4, Honeyman et al. teach the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence (see Figure 3).

With regard to claim 5, Honeyman et al. teach further including a nonhybridizing spacer between the primer sequence and the blocking sequence (see Figure 3, where the nonhybridizing sequence is the sequence which anneals back to the normal sequence therefore it does not hybridize with the target sequence carrying the mutation).

With regard to claim 9, Honeyman et al. teach the spacer is nucleotidic (see p. 735 under *Materials and Methods*).

With regard to claim 12, Honeyman et al. teach the spacer is an oligomeric segment comprised of a recurring single nucleotide (see p. 735 under *Materials and Methods*).

With regard to claim 13, Honeyman et al. teach the probe sequence and the spacer are separated from each other by a means for halting transcription therebetween (see p.735 under *Materials and Methods* and p. 736 col. 2, where the primer sequence is separated from the snap back sequence, which meets the structural limitation recited in the claim because the recitation "by a means for halting transcription therebetween" is functional language, which is inherently met by the primer of Honeyman).

With regard to claim 14, Honeyman et al. teach the means for halting transcription is an arresting linker (see p.735 under *Materials and Methods* and p. 736 col. 2, where the primer sequence is separated from the snap back sequence which meets the structural limitation recited in the claim because the recitation "an arresting linker" is functional language which is inherently met by the primer of Honeyman).

With regard to claim 26, Honeyman et al. teach an amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence (s see p.735 under *Materials and Methods*).

```
                    GC
                    G C
                    A T
                   T A
                    C G
Target        XXXTTCCTTA  TCCATAGGCAA
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Honeyman's primer CTTAAGGAAT*GATCC*GCATGGG

The underlined nucleotides in Honeyman's primer correspond to clause (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; The nucleotides in italics correspond to the blocking sequence as functionally defined in clause (b) a blocking sequence substantially complementary to a segment of the secondary structure forming

region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest. When the primer of Honeyman hybridizes to the target the secondary structure of the target will be disrupted and the site in the underlined region will be available for detection or amplification. The primer of Honeyman et al. inherently possesses the functional properties of clause (b) for this particular target.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of Laibinis et al. (US 2002/0028455).

The teachings of Honeyman et al. are discussed above.

Honeyman et al. do not teach all the limitations of claims 6-8, 15 and 16.

Laibinis et al. teach the spacer is non-nucleotidic (see paragraph 0014), the spacer is comprised of a synthetic hydrophilic oligomer (see paragraph 0014, where the linker is comprised of chains of alkylene units, specifically polyethylene gylcol, making it hydrophilic) and the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide (see paragraph 0014).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Primer, as taught by Honeyman et al. with the concept of varying the linkers as taught by Laibinis et al. Laibinis et al. teach a variety of linkers can be used in a primer molecule. A skilled artisan would readily understand from reading Laibinis et al. that type and lengths of linkers can

be successfully varied. An ordinary practitioner would have been motivated to use the Primer, as taught by Honeyman et al. with the concept of varying the linkers as taught by Laibinis et al. in order to successfully choose a linker for a primer.

5. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of Switzer et al. (Biochemistry, 1993).

The teachings of Honeyman et al. are discussed above.

Honeyman et al. do not teach all the limitations of claims 10-11.

Switzer et al. teach the non-natural nucleotides of iso-G and iso-C in a primer molecule (see the abstract and Fizure 3)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Primer, as taught by Honeyman et al. with the concept of non natural nucleotides as taught by Switzer et al. Switzer et al. teach non natural nucleotides can be incorporated into a template uisng the Klenow fragment of DNA polymerase. Additionally, Switzer et al. teach non natural bases are useful in a laboratory setting. A skilled artisan would readily understand from reading Switzer et al. that the non natural nucleotides of iso-C and iso-G can be successfully used in primer oligonucleotides. An ordinary practitioner would have been motivated to use the Primer, as taught by Honeyman et al. with the concept of non natural nucleotides as taught by Switzer et al. Switzer et al. in order to increase specificity of the oligonucleotide for a target.

6. Claims 17-18, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of Beattie et al. (USPN 6,268,147, 2001).

The teachings of Honeyman et al. are discussed above.

Honeyman et al. do not teach all the limitations of claims 17 and 18.

Beattie et al. teach further comprising a detectable label (see col. 20 lines 33-66 to col. 21 lines 1-37) and Beattie et al. teach the detectable label is a radioactive isotopes (see col. 20 lines 33-66 to col. 21 lines 1-37, where ^{32}P is the label).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Primer, as taught by Honeyman et al. with the concept of labeling as taught by Beattie et al. Beattie et al. teach labels can be used in a primer molecule. A skilled artisan would readily understand from reading Beattie et al. that labels can be successfully used in a primer molecule. An ordinary practitioner would have been motivated to use the Primer, as taught by Honeyman et al. with the concept of labeling as taught by Beattie et al. in order to successfully label a primer for use in subsequent detection applications.

7. Claims 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of the Stratagene Catalog (1988).

The teachings of Honeyman et al. are described above

Honeyman et al. do not teach or suggest a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dual purpose primer for amplification as taught by Honeyman et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually

far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2). The other service provided in a kit is quality control" (page 39, column 1).

8. Claims 1and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (USPN 5,030,557).

Hogan et al. teach using a combination of a primer and a "helper" sequence in which the "helper" sequence acts functionally to block intramolecular secondary hairpin target formation to facilitate PCR of the target regions (see col. 4). While Hogan et al. do not teach the primer and helper are combined in a single sequence as instantly claimed. However one of ordinary skill in the art would have been motivated to combine the two sequences of Hogan et al. into a single sequence as instantly claimed because primer design is routine and obvious to a skilled artisan. A skilled artisan would recognize there are two ways to combine the sequences of Hogan et al.; with a linking sequence or directly as a single contiguous sequence. A skilled artisan would have been motivated to combine the two sequences of Hogan et al. into a single primer sequence because a single sequence results in a lower cost assay which is less labor intensive and more practical.

Response to Arguments

9. Applicants' arguments filed August 23, 2010, have been fully considered but they are not persuasive. Applicants' argue, beginning on p. 11 of the response, the claimed invention is not directed to a procedure by which an SNP site becomes part of the secondary structure formed in a single stranded nucleic acid sequence but the invention is drawn to primers and probes that disrupt secondary structures that conceal SNPs. This argument is not persuasive because it is irrelevant what procedure is employed

by Honeyman et al. because Applicants are claiming products, specifically nucleic acids. Honeyman et al. teach the instantly claimed nucleic acids and it is therefore irrelevant how Honeyman et al. uses the nucleic acids. As outlined in the rejection above, Honeyman et al. teach the instantly claimed nucleic acids. The diagram above illustrates how the nucleic acid of Honeyman et al. meets all of the structural and functional limitations recited in the claims when the appropriate target is present. Applicants argue Honeyman et al. do not teach the (a) a primer sequence complementary to a segment *of the target nucleotide sequence* other than the secondary structure forming region and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in *an amplicon* thereby enabling detection and amplification of the site of interest. This argument is not persuasive because the structural limitations are in the target nucleic acid or the amplicon not the primer or the probe nucleic acids which are what is claimed. As illustrated above, the primer of Honeyman et al. has (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; The nucleotides in italics correspond to the blocking sequence as functionally defined in clause (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest. When the primer of Honeyman hybridizes to the target the secondary structure of the target will be disrupted and the site in the underlined region will be available for detection or amplification. The primer of Honeyman et al. inherently possesses the functional properties of clause (b) for this particular target.
Applicants argue the site of interest disclosed by Honeyman et al. does not appear in the target sequence used in the illustration. Applicants argue the complement does not appear in the G2 primer. These arguments are not persuasive because the complement and the site of interest are not claimed. The complement and the site of interest occur in the target and Applicants are claiming the primer not the

target. Honeyman et al. is not relied on for teaching the target nor does Honeyman et al. need to teach the target as the target is not what is claimed. With regard to Applicants' request for an affidavit, the Examiner notes that there is no basis in MPEP § 2144 which requires the Office to supply an affidavit when the facts are provided directly in the prior art document(s). None of the facts relied upon in the 102 rejection are the personal knowledge of the examiner. Instead, as noted in the 102 rejection recited above, the facts are expressly stated within the reference(s). The Examiner at no point in the rejection indicated the use of personal knowledge in applying the references. This line of argument is inappropriate.

Applicants' arguments with respect to the 103(a) rejections using Honeyman et al. are moot in view of the further explanation of the application of Honeyman et al.

With respect to the 103(a) rejection over Hogan et al. Applicants argue there is no motivation to prepare a single probe. This argument is not persuasive because as stated in the rejection above primer design is routine and obvious to a skilled artisan. A skilled artisan would recognize there are two ways to combine the sequences of Hogan et al.; with a linking sequence or directly as a single contiguous sequence. A skilled artisan would have been motivated to combine the two sequences of Hogan et al. into a single primer sequence because a single sequence results in a lower cost assay which is less labor intensive and more practical.

Summary

10. No claims were allowable.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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/Heather G. Calamita/
Primary Examiner, Art Unit 1637